Docket No. 47,653.2 (1789)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	J.C. Houck, et al.		
Serial Number:	09/190,043	Art Unit:	1631
Filed:	November 10, 1998	Examiner:	M. Borin
For:	SMALL PEPTIDES AND METHODS FOR TREATMENT OF ASTHMA AND INFLAMMATION		

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on June 9, 2000.

Jennifer K. Holmes

Honorable Assistant Commissioner for Patents
Washington, DC 20231

Sir:

DECLARATION OF JAMES CLAGETT

I, James Clagett, hereby declare that:

1. I am a citizen of the United States of America residing at 5615 139th Avenue SE, Snohomish, Washington 98290.

2. I hold a Ph.D. in microbiology from the University of Nebraska. I have over 30 years experience in research and development related to microbiology, particularly in the fields of immunology and immunopathology. A copy of my curriculum vitae is attached hereto as Attachment A.

3. Since 1997, I have been a consultant providing scientific expertise to the biotechnology and pharmaceutical communities.

4. I personally performed or directly oversaw the experiments which produced the results presented and discussed herein.

5. I have read and understand the Office Action of January 12, 2000, including the references cited therein.

6. The present invention is directed to a method for treating an allergy reaction in a mammal comprising administering a peptide having the formula f—Met-Leu-X, wherein X is selected from the group consisting of Tyr, Tyr-Phe, Phe-Phe and Phe-Tyr.

7. Based on my knowledge and experience in the field, it is my opinion that it is well known to those skilled in the art that formyl methionyl peptides have pro-inflammatory activity. Additionally, it is well documented in the literature that not all formyl Met peptides are functionally equivalent.

8. However, surprisingly, it has been found by present applicants that certain formyl methionyl peptides, particularly f--Met-Leu-Phe-Phe, can provide

a useful anti-allergenic effect.

9. In Example 12 of the present application OVA was used to induce an allergic response in mouse airway passages. Treatment with f-Met-Leu-Phe-Phe alleviated the allergic response. Based on my knowledge and experience in the field, it is my opinion that such a response to the treatment could not have been predicted by one skilled in the art based on any prior art teachings.

10. In addition, the following experiments have been performed under my direction and control.

Briefly, female Balb/CJ mice were injected subcutaneously into the dorsum of the feet with either (a) 10 μg fMLP peptide, (b) 200 μg of fMLP, (c) 200 μg fMLP and 200 μg FMLPP simultaneously or (d) vehicle alone (4% DMSO in Tyrode's solution) as a control. The animals were sacrificed at 10 or 30 minutes post-injection and the feet collected for histological examination. The cutaneous soft tissues were dissected from the feet and embedded in paraffin. 5-7 μ sections were cut and stained with H&E for the detection of cellular content and location within the muscularis and dermis. The results are illustrated in the figures in Attachment B.

11. Figure 1 shows stained tissue sections harvested from mice 10 minutes after injection with 10 μg of fMLP into the subcutaneous layers of the

skin on the dorsum of the feet. Polymorphonuclear cells (PMNs) have migrated into the interstitium and have attached to vessel walls.

Panel A (x160) shows numerous PMNs (arrows) located within the intercellular matrix and the connective tissue appears edematous and slightly hemorrahagic.

Panel B (x160) shows the extravascular migration of leukocytes from an oblique section of a small blood vessel in the muscularis region.

Panel C (x320) shows the extravascular migration of neutrophils from another blood vessel.

12. Figure 2 compares stained tissue sections harvested from mice 30 minutes after injection with (i) 200 μg of fMLP alone, (ii) 200 μg fMLP and 200 μg fMLPP simultaneouly or (iii) vehicle alone into the subcutaneous layers of the skin on the dorsum of the feet.

Panel A (x100) shows the results of injection with 200 μg of fMLP alone. A massive cellular infiltration and a reddish reaction material is observed in the interstitium of the skin. Many leukosytes are in the extravascular spaces and associated with small blood vessels (arrows).

Panel B (x100) shows the results of simultaneous injection with 200 μg of fMLP and 200 μg of fMLPP. fMLPP reduced the cellular infiltration observed when fMLP was injected alone (see panel A). The vessels have no PMNs inside or outside (arrows).

Panel C (x100) shows the results of tissues harvested from control animals injected with vehicle (4% DMSO) alone. No cellular infiltration is seen and no PMNs are observed in association with the small blood vessels (arrows).

13. From these experiments, it can be concluded that fMLP (prior art) administration into the skin of mice produced an intense vascular and extravascular accumulation of inflammatory cells, largely neutrophils. Simultaneous administration of fMLPP (invention) with fMLP (pro-inflammatory) reduced the inflammatory response to near normal levels.

14. This experiment is further evidence that all formyl methionyl peptides are not equivalent.

15. Based on my knowledge and experience in the field, it is my opinion that one skilled in the art would readily conclude from these experiments that the prior art peptide, fMLP, has pro-inflammatory or allergy stimulating activity and that the peptide of the current invention, fMLPP, has anti-inflammatory or anti-allergenic activity.

16. Based on my knowledge and experience in the field, it is my opinion that the surprising and unexpected anti-inflammatory and anti-allergenic

results achieved with the peptides of the present invention would not have been obvious to those skilled in the art.

17. It is my understanding that the Patent Examiner contends that the claims do not reasonably provide enablement for pharmaceutical use of f-met peptides in the absence of exposure to such pro-inflammatory agents.

18. It is necessary to induce an allergenic response in order to test compound for its effect on treating the allergenic response. Pre-administration of pro-inflammatory agents was used as a way to generate an experimental model of an allergy reaction. The present invention is directed to a method for treating an allergy reaction. In other words, the method is directed to treating a mammal which has been exposed to an allergy stimulating agent.

19. The application provides considerable description for treating allergy reaction using formyl Met peptides, including dosage. Further, an extensive experimental section presents detailed descriptions and results of *in vitro* and *in vivo* experiments showing the administration of formyl Met peptides of the invention can inhibit mast cell degranulation, eosinophil infiltration and mucus accumulation. Data is presented from a mouse model of asthma (pages 21-40). Furthermore, the dosages used for treatment of the mouse model of asthma (for example, at page 31, lines 10-14, 5-10 μg/kg of HK-X was administered)

and the mouse model of arthritis (for example, at page 43, lines 15-30, 0.4 mg/kg or 4 mg/kg of HK-X was administered) were disclosed and the dosages are within the effective range indicated in the specification at page 12.

20. Based on my knowledge and experience in the field, it is my opinion that one skilled in the art would be fully enabled to use the f-met peptides described in the application for treatment of an allergy reaction. At most, routine experimentation is required to determine the optimum dose.

21. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Codes, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

6/9/2000
Date

James Clagett

Attachment A

JAMES A. CLAGETT, Ph.D.
5615 139th Avenue SE
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EXPERIENCE:

CLAGETT CONSULTING
5615 139TH AVE SE
SNOHOMISH, WASHINGTON, 98290

Founder and Partner: January 1, 1997 to present.

Providing quality expertise to the biotechnology and pharmaceutical communities. Lead an assembled group of individuals with experience in regulatory affairs, preclinical and clinical studies. The team has worked together for an average of 3 years and was instrumental in bringing products from research through production for GenSci Regeneration Laboratories Inc., Irvine, CA. Current list of clients includes Histatek, LLC, San Francisco, CA and BioTherapeutic Computers, Seattle, WA.

BIOCOLL LABORATORIES INC.
562 1ST AVENUE SOUTH
SEATTLE, WASHINGTON, 98104

Vice President and Scientific Director: January 1993 to August 1, 1997.

Responsible for implementing and maintaining the company's overall scientific plan. Initiated the development of the company's first product, the Tissue Bone Matrix sponge and the DynaGraft family of products and human banked tissue. Supervised the writing and implementation of the Standard Operating procedures or the TBM sponge. Initiated the scientific research of new products and managed numerous consultants supporting the company's scientific strategic plan. Carried the company from conceptual design of products through introduction to the marketplace including continuous interaction with FDA.

DENTAL DIAGNOSTIC SERVICES
2000 116TH AVENUE NE.
BELLEVUE, WASHINGTON 98004

Founder and Officer: December 1992 through January 1, 1993

Responsible for taking the company from no revenues to profitability in one year. Company had over 450 clients using the sterility testing services of Dental Diagnostic Services.

THE DENTAL RESOURCE INC.
2000 116TH AVENUE NE,
BELLEVUE, WASHINGTON 98004

Consultant: October 1990 to December 1992

Responsible for developing product concept for novel water filtration device for dental offices. Participated heavily in selling devices to dental practitioners.

ULTRA DIAGNOSTICS CORPORATION
4526 11th Avenue NE, Seattle, Washington, 98108

Chief Executive Officer, President, and Scientific Director: December 1988 to December 1989.

Responsible for implementing and maintaining the company's overall business plans. Maintained on-going communications with investors. Supervised the recruitment of research and development personnel and management finance, administration, marketing and regulatory functions. Responsible of business development where a contract of $500,000 for research and development of new reagents was concluded. Responsible for continued venture funding of approximately $900,000. Maintained ongoing contact with key administrative and upper management individuals of the biotechnology and academic sectors in the Northwest.

President and Scientific Director: December 1984 to December 1988. Implemented the company's research and development plans and assisted the Chief Executive Officer with business development functions where research and development contracts worth $500,000 were secured. Coordinated the use of the Scientific Advisory Board and recruited and hired key scientific personnel. Assisted the Chief Executive Officer in capital formation from "seed" through venture financing. The capital raised was in excess of $4 million.

UNIVERSITY OF WASHINGTON
Schools of Medicine and Dentistry
Seattle, Washington, 98105

Affiliate Professor: 1987 to 1989.

Taught a course in Immunology and Immunopathology to Graduate Dental Students.

Professor of Periodontics and Microbiology and Immunology: 1983 to 1987

Associate Professor of Periodontics and Microbiology and Immunology: 1978 to 1983.

Research Assistant Professor of Periodontics and Microbiology and Immunology: 1973 to 1978

Taught graduate and undergraduate Immunology and Immunopathology to Microbiology and Immunology majors as well as participated in team teaching to dental and medical students. Received well above average reviews of teaching skills by students. Maintained a research laboratory with technicians, 2 doctoral and 6 masters' students. Obtained research support averaging $150,000 per year and served on the Faculty Senate and the Human Subjects Review Committee. Served as a member on 15 doctoral and masters thesis committees.

PROFESSIONAL ASSOCIATIONS:

Editorial Board of Journal of Dental Research
Biomedical Research Support Grant Committee
American Association of immunologists
Sigma Xi

EDUCATION:

Scripps Clinic and Research Foundation	Postdoctoral Fellowship	1973
University of Nebraska	Ph.D.	1970
DePauw University	BS	1964

PUBLICATIONS

Clagett, J. A., Engelhard, W. E. The immunosuppressive activity of the 3-a1 fraction of papain. J. *Bacteriol.* 93:19492,1967.

Peter, H. H., **Clagett, J. A.,** Feldman, J. D., and Weigle, W. 0. Rabbit antiserum to brain associated thymus antigens of mouse and rat. I. Demonstration of antibodies cross-reacting to T cells of both species. J. *Immunol.* 110:1077, 1973.

Clagett, J. A., Peter, H. H., Feldman, J. D., and Weigle, W. 0. "Rabbit antiserum to brain associated thymus antigens of mouse and rat. II. Detection of species specific and theta related determinants J. *ImmunoL* 110:1085 ,1973.

Clagett, J. A., Tokuda, S., Engelhard, W. E. Chymopapain C., an immunosuppressive protease: I. Purification and characterization. *Proc. Soc. Exp. Biol. Med.,* 145:1250,1974.

Clagett, J. A., Tokuda, S., and Engelhard, W. E. Chymopapain C., an immunosuppressive protease: II. Effect on the primary and secondary response in mice. *J. Immunol.* 112:1669, 1974.

Clagett, J. A., and Weigle, W. 0. Role of T- and B-lymphocytes in the termination of unresponsiveness to autologous thyroglobulin. J. *Exp. Med.* 139:643,1974.

Clagett, J. A., Wilson, C. B, and Weigle, W. 0. Interstitial immune complex in mice: The role of autoantibody to thyroglobulin. J. *Exp. Med.* 140:1439,1974.

Huang, L. Y., Stern, I. B., **Clagett, J. A.,** and Chi, E. Y. Two polypeptide chain constituents of the major protein of the comified layer of newbom rat epidermis. *Biochemistiy* 14:3573,1975.

Engel, L. D., Van Epps, D., and **Clagett, J. A.** In vivo and in vitro studies on possible pathogenic mechanisms of Actinomyces viscosus. *Infection and Immunity* 14:548 ,1976.

Storb, U., Hager, L., Putnam, D., Buck, L., Marvin, S., Farin, F., and **Clagett, J.** Sequences related to immunoglobulin kappa chain messenger RNA T cells. *Proc. Nat'l. Acad. Sd. U.S.A.* 73:2467,1976

Dale, B., Stern, I. B., and **Clagett, J. A.** Initial characterization of the proteins of keratinized epithelium of rat oral mucosa. *Arch. Oral Biol* 22:75 ,1977.

Putnam, D., Storb, U., and **Clagett, J.** Synthesis of kappa chains from thymus RNA by cell free translation. Proceedings of UC and ICN Meeting, March, 1977. In Regulatory Genetics of the Immune System ICN-UCLA Symposia on Molecular and Cellular Biology. 6:71 ,1977.

Press, 0. W., Rosse, C. and **Clagett, J. A.** The distribution of short-lived and long-lived T-, B-and null-lymphocytes mouse bone marrow, thymus, lymph node and spleen. *Cellular Immunol.* 33:114-124,1977.

Morton, T., **Clagett, J. A.,** and Yavorsky, D. The role of immune complexes in chronic periapical lesions. J. *Endodontics* 3:261,1977.

Engel, L. D., **Clagett, J. A.,** Page, R. C., and Williams, B. Mitogenic activity of Actinomyces viscosus: I. Effects of murine B- and T-lymphocytes and partial characterization. J. *Immunol.* 118:1466,1977.

Press, 0. W., Rosse, C., and **Clagett, J. A.** Phytohemaglutin-induced differentiation and blastogenesis of precursor T-cells from mouse bone marrow. *J Exp. Med.* 146~735 *1977.*

Press, 0. W., Rosse, C., and **Clagett, J. A.** Anti-θ brain antisera bind primarily to non-T cells in mouse bone marrow. *Proc. Soc. Exp. Biol. Med* 156:485 ,1977.

Clagett, J. A., and Page, R. C. Insoluble immune complexes and periodontal diseases in man and the dog. *Arch. Oral Biol.* 23:153,1978.

Clagett, J. A., and Engel, L. D. Polyclonal activation: A form of primitive immunity and its possible role in chronic inflammatory diseases. *Develop. and Comp. Immunol.* 2:235,1978.

Page, R. C., Engel, L. D., **Clagett, J. A.,** and Narayanan, A. S. Chronic inflammatory gingival and periodontal disease. J. *Am. Med. Assoc.* 240:545,1978.

Rosse, C., Cole, S. B., Appleton, C., Press, 0. W., and **Clagett, J. A.** The relative importance of the bone marrow in the production and dissemination of B-lymphocytes. *Cell Immunol.* 37:254 ,1978.

Sims, T., **Clagett, J. A.,** and Page, R. C. Effects of cell concentration and exogenous prostaglandin on the interaction and responsiveness of human peripheral blood leukocytes. *Clin. Immunol. and Immuno path. 12:* 150,1979.

Page, R. C., **Clagett, J. A.**, Engel, L. D., and Sims, T. Effects of prostaglandin on the antigen and mitogen-driven responses of peripheral blood lymphocytes from patients with adult and juvenile periodontitis. *Clin. Immunol. and Immunopath,* 11:77 ,1978.

Torbinejab, M., **Clagett, J.,** and Engel, D. A cat model for the evaluation of mechanisms of bone resorption: induction of bone loss by stimulated immune complexes and inhibition by Indomethacin. *Calcif. Tissue Res..* 29:207,1979.

Putnam, D., **Clagett, J.,** and Storb, U. Immunoglobulin synthesis by T cells: quantitative and qualitative aspects. J *Immunol.* 124:920,1980.

Storb, U., Near, R., **Clagett, J**. Immunoglobulin messenger RNA's of T lymphocytes. *Molecular Immunology* 17:474, 1980.

Engel, L. D., Chi, E., and **Clagett, J. A.** Mitogenic activity of Actinomyces viscosus. II. Induction of DNA and immunoglobulin synthesis in rabbit B lymphocytes. *Dev. Comp. Immunol* 4515 1980.

Engel, L. D., Schroder, H. E., Gay, R. G., and **Clagett, J. A.** Fine structure of cultured human gingival fibroblasts and demonstration of simultaneous synthesis of types I and III collagen. *Arch. Oral Biol.* 25:283 ,1980.

Clagett, J. A., Engel, L. D., and Chi, E. In vitro expression of immunoglobulin M and G subclasses by murine B lymphocytes in response to a polyclonal activator from Actinomyces viscosus. *Infect. Immunity* 1980.

Korotzer, T. I., **Clagett, J. A.,** Kolb W. *P.,* and Page, R. C. Complement dependent induction of DNA synthesis and proliferation of human diploid fibroblasts J.*Cell Physiol.* 105:503, 1980.

Landreth, K. S, McCoy, K. L., **Clagett, J. A.**, Bollum, F. J., and Rosse, C. Deficiency in terminal deoxynucleotidyl transferase-positive cells associated with severe autoimmune disease. *Nature* 290~409 *1981.*

Engel, L. D., Clark, E. A., Held, L., Kimball, H., and **Clagett, J. A.** Immune responsiveness of SM/J mice. Cellular characteristics and genetic analysis of hyperresponsiveness to B cell mitogens. J *Exp. Med.* 154:726,1981.

Landreth, D. S., Ross, C., and **Clagett, J. A.** The myelogenous phase in the production and maturation of primary B lymphocytes in the mouse. J. *Immunology* 127:2027, 1981.

McCoy, K. L., **Clagett, J. A.,** and Chi, E. Abnormal maturation of mono-nuclear phagocytes associated with autoimmunity in motheaten mice. *Oral Immunogenetics and Tissue Transplantation,* G. R. Riviere and W. H. Hildemann, eds. Elsevier/North Holland, 1982.

McCoy, K. L., Chi, E., Engel, D., and **Clagett, J.** Abnormal in vitro proliferation of splenic mononuclear phagocytes from autoimmune motheaten mice. J. *Immunology* 128:1797,1982.

McCoy, K. L., and **Clagett, J. A.** Accelerated rate of mononuclear phagocyte maturation in autoimmune motheaten mice. *Fed. Proc..* 41:559,1982.

Engel, D., Clark, E. A., Chi, E., and **Clagett, J.** *Genellc aspects of responsiveness to B cell mitogens in mice. Oral Immunogenetics and Tissue Transplantation,* G. R. Riviere, ed. Elsevier/North Holland, 1982.

McCoy, K. L., **Clagett, J. A.**, Engel, L. D., and Chi, E. Accelerated rate of mononuclear phagocyte production in vitro by splenocytes from autoimmune motheaten mice. *Am J. Pathol.* 112:18 1983.

Clagett, J. A., and Engel, L. D. *Polyclonal B-cell activation in response to* Actinomyces viscosus *- its nature and genetics.* In Biological, Biochemical and Biomedical Aspects of Actinomycetes. Edited by L. Ortiz-Ortiz, L. F. Bojalil and V. Yakoleff. Academic Press, Orlando, pp.61-71,1984.

McCoy, K. L., Nielson, K., and **Clagett, J.** Spontaneous Production of Colony-Stimulating Activity by Splenic Mac-I Antigen-Positive Cells from Autoimmune Motheaten Mice. J *Immunology* :272, 1984.

Engel, D., Monzingo, S., Rabinovitch, P., **Clagett, J.,** and Stone, R. Mitogen-induced hyperproliferation response of peripheral blood mononuclear cells from patients with severe generalized periodontitis: lack of correlation with proportions of T-cells and T-cell subsets.. *Immunopathol Clin. Immunol* 30:374, 1984.

McAnulty, K., Stone, R., Hastings, G., **Clagett, J.**, and Engel, D. Immunoregulation in severe generalized periodontitis. *Clin. Immunol. Immunopathol* 34:84 1985.

ABSTRACTS

Clagett, J. A. Cellular collaboration and specificity in murine thyroiditis. *Fed. Proc.* 31:743, 1972.

Peter, H. H., **Clagett, J. A.,** Wilson, C. B., and Feldman, J. D. Rabbit antisera to brain associated thymus antigens of mouse and rat. *German Soc. Immunol.,* 1972.

Engel, L. D., **Clagett, J, A.,** and Page, R. C. A possible role for bacterial mitogens in chronic inflammatory periodontal disease. *J Periodontol.*,1975.

Engel, L. D., **Clagett, J. A.,** and Page, R. C. Response of mouse spleen cells to Actinomyces viscosus antigens. *FASEB,* 1975.

Clagett, J. A., Booth, R., and Page, R. C. Role of immune complexes in human periodontitis. *IADR,* 1976.

Suzuki, J. B., **Clagett, J. A.** Sims, T., and Page R. C. Analysis of the cell-cell interactions in the blastogenic response of lymphocytes of periodontal disease patients. *IADR,* 1979.

Putnam D. L. **Clagett, J. A.** Different proliferation and immunoglobulin responses of B cells to four mitogens. *FASEB,* 1980.

McCoy, K. Rosse, C., and **Clagett J.** The cellular composition and B cell mitogen responsiveness of lymphoid cells of motheaten mice (me/me). *FASEB,* 1980.

Landreth, K. S., Rosse, C., and **Clagett, J.** Evidence for a lineage relationship between cytoplasmic micron+ micron-, and surface micron+ B lymphocytes in adult murine bone marrow. *FASEB,* 1980.

Clagett, J. A., klimpel, K., Klimpel, G., and McCoy, K. Ia-negative murine B cells: Proliferative and differentiative capacity in vitro. *IADR,* 1981.

Engel, D., Kimbalil H., Clark, E., and **Clagett, J.** Genetic control of high responsiveness to B-cell mitogens. *IADR,* 1981.

McCoy, K., Rosse, C., and Clagett, J. Abnormal proliferation of splenic macrophages from autoimmune motheaten mice. *FASEB,* 1981.

Engel, D., Monzingo S., Rabinovitch, P., **Clagett, J.** Mitogen-induced hyperproliferation response of lymphocytes from patients with severe generalized periodontitis: Lack of correlation with proportions of T--cell subsets. *FASEB* 1982.

Windsor, N., **Clagett, J. A** Novel effector system: Bone marrow transformation activity produced by a T:T hybridoma. *FASEB,* 1984.

Beneveniste, R. E., Stromberg, K., Arthur, L. 0., Giddens, W. E. Jr., Ochs, H. D., Morton, W. R., and **Clagett, J. A.** Transmission of Retroperitoneal Fibromatosis (RF) by SAIDSD/Washington retrovirus. *International Academy of Pathology,* 1985.

FIGURE 2

Comparison of the induction of PMN diapedesis in the dermal tissues of mice when injected with HK-X simultaneously with fMLP.

PANEL A. Thirty min after injection of 200 ug of fMLP, a massive cellular infiltration and a reddish reaction material is observed in the interstitium of the skin. Many leukocytes are in the extravascular spaces and associated with small blood vessels (arrows). X100

PANEL B. The simultaneous injection of HK-X reduced the cellular infiltration observed when fMLP was injected alone (See panel A). The vessels have no PMNs inside or outside (arrows). X100

PANEL C. Tissues harvested from an animal which received only vehicle show no cellular infiltration. No PMNs are observed in associatioon with the small blood vessels (arrows). X100

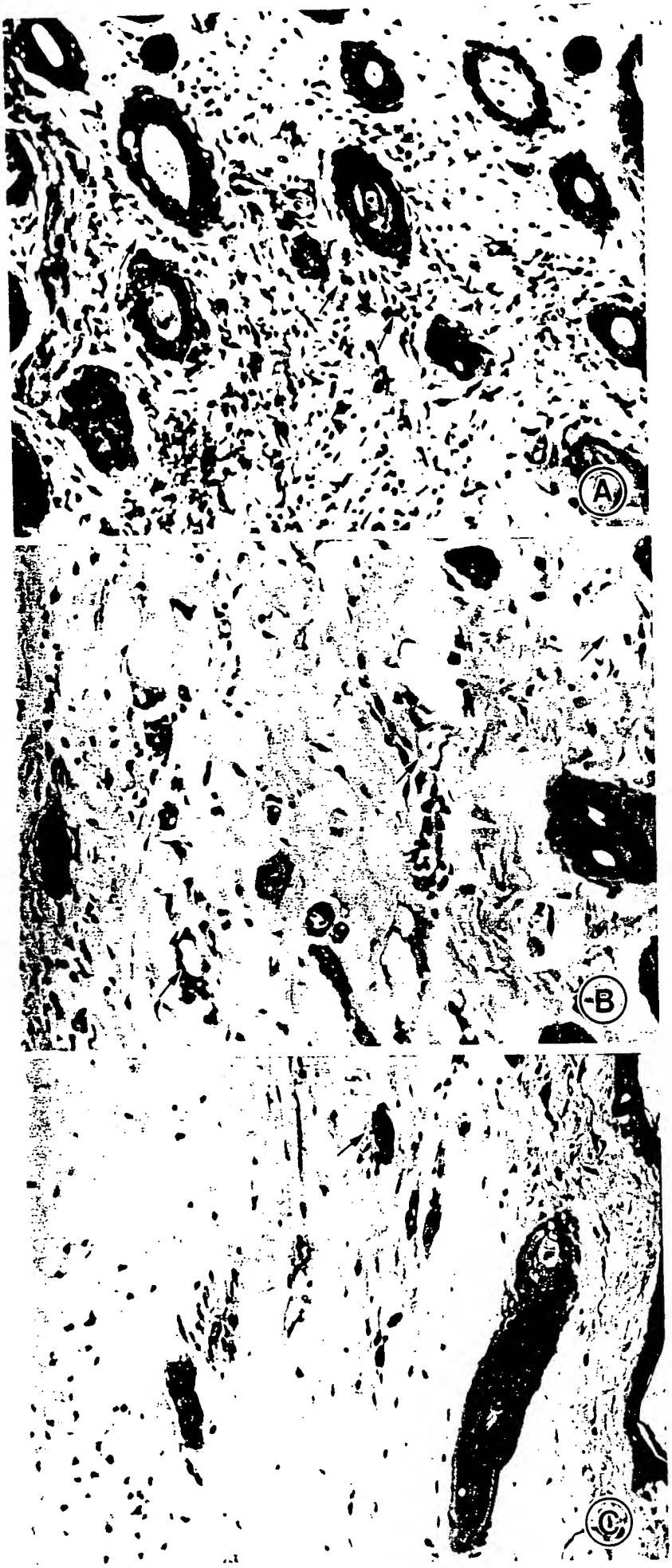

FIG. 2

FIGURE 1

Ten minutes after injection of 10 ug of fMLP into the subcutaneous layers of the skin on the dorsum of mice feet, PMNs have migrated into the interstitium and have attached to vessel walls.

PANEL A. Numerous PMNs (arrows) are located within the intercellular matrix and the connective tissue appears edematous and slightly hemorrahagic. X160

PANEL B. An oblique section of a small blood vessel in the muscularis region shows the extravascular migration of leukocytes (arrows). X160

PANEL C. At higher magnification, another vessel shows the diapedesis of neutrophils (arrows). X320

Attachment B

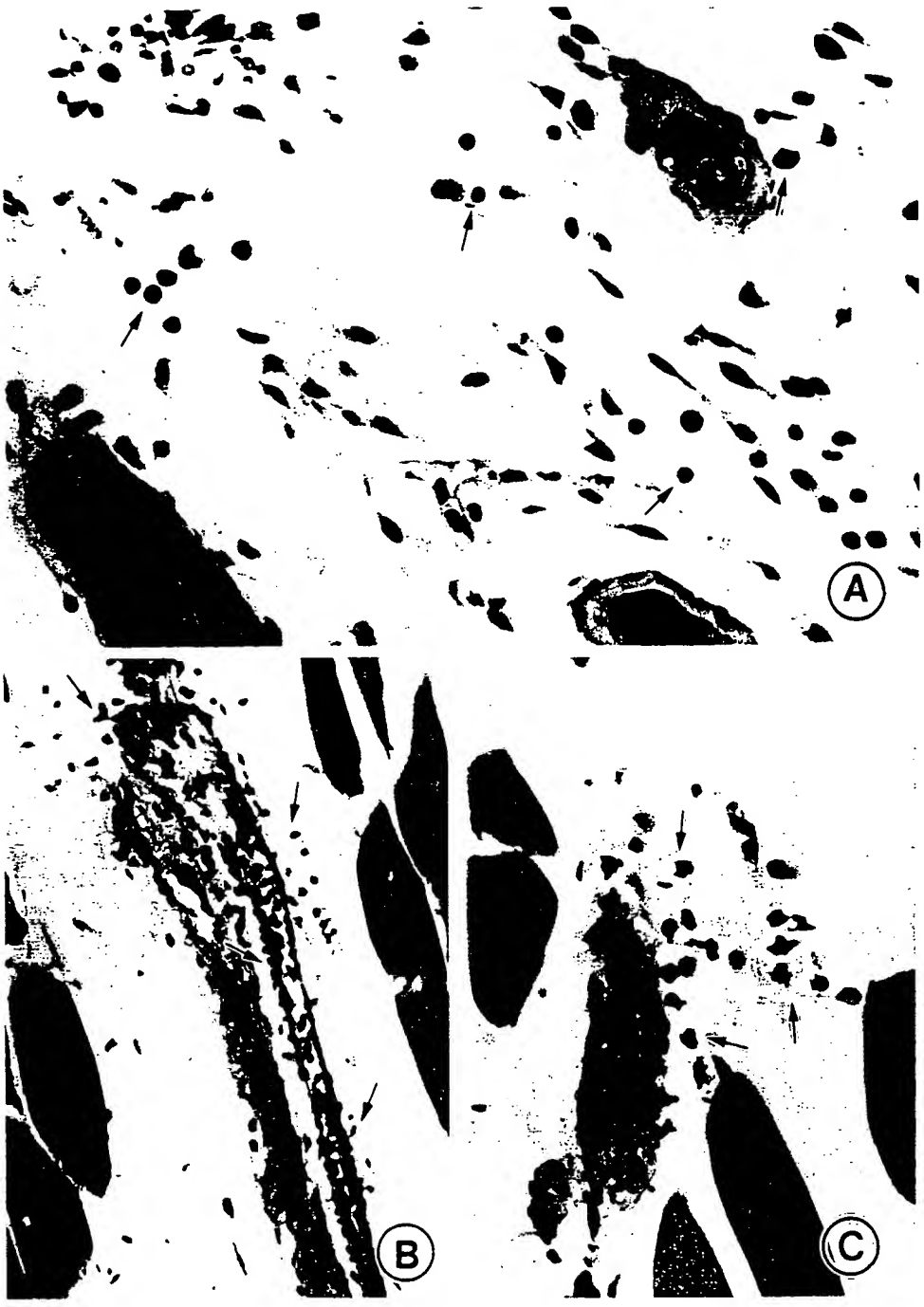

FIG. 1